Multistage Models and Primary Prevention of Cancer [1]

Nicholas E. Day [2] *and* Charles C. Brown [3, 4]

ABSTRACT—Removal of carcinogenic exposures should reduce the subsequent risk for developing cancer. Of interest are the extent of the reduction and the speed with which it takes place. Multistage models with more than two stages for tumor development predict different patterns of changing risk following removal of a carcinogenic exposure, depending upon the stage in the process that the carcinogen predominantly affects. The fall in risk following removal of an early-stage carcinogen is only slowly evident, whereas removal of a late-stage carcinogen leads to a more rapid reduction in excess risk. Experimental and epidemiologic data are reviewed, and both early- and late-stage effects are seen. The long-term danger arising from entry into the environment of early-stage carcinogens is discussed, and it is shown that by the time human evidence that a hazard does exist becomes available, those already exposed may well have accumulated their fully effective doses.—JNCI 64: 977-989, 1980.

Mathematical models derived from a multistage theory for the process of cancer development are strikingly successful in describing many experimental and epidemiologic observations. The marked regularity of age-incidence curves for most spontaneous human tumors of epithelial origin (*1*) and similar regularity for many tumors induced experimentally by continuous exposure to chemical carcinogens (*2, 3*) are predicted by multistage models. Furthermore, the increase of incidence with age is predicted to be a reflection of increasing time since exposure began rather than an aging phenomenon, a prediction confirmed experimentally (*4*); the increase in incidence of lung cancer as a function of duration of smoking behaves similarly (*5*). Power low-dose response curves, with exponent 1 to 2, are often observed experimentally, as expected from multistage models (*6*). The recent demonstration that the increase in lung cancer risk fits better to the square of daily cigarette consumption, rather than linearly, accords with the apparent requirement that both an early and a late stage in the carcinogenic process are affected by tobacco smoke (*7*). The frequent epidemiologic finding that the joint action of two risk factors is multiplicative rather than additive is also easily interpretable on multistage theory (*8*), different stages being affected by the different factors. Demonstration of the phenomena of initiation and promotion provides direct evidence that both early- and late-stage events can influence tumor incidence. There is thus a considerable body of data giving empirical support to multistage models, in which some or all of the stages can be affected by external agents.

Whittemore (*9, 10*) has recently explored in general fashion the changes in the age-incidence curve that multistage theory would predict following changes in the level of exposure to carcinogenic agents. Particular attention was given to the stage in the process that is affected by the carcinogen. Our purpose here is to explore in more detail the changes in risk after cessation of exposure and to show that both experimentally and epidemiologically two very different types of behavior are observed: one corresponding to early-stage carcinogenesis, the other to late-stage carcinogenesis. This approach may provide a framework for predictions of the benefits one might expect from measures taken to reduce exposures and may assist in formulating a rational basis for intervention strategy.

ARMITAGE-DOLL MODEL OF CARCINOGENESIS

The multistage model for carcinogenesis as proposed by Armitage and Doll (*11*) assumes that a single cell can generate a malignant tumor only after it has undergone a certain number, e.g., k, of heritable changes. These cellular changes can be thought of as representing stages in the carcinogenic process that are characterized as being of slow and improbable occurrence. This model assumes that the tissue in question initially consists of normal cells, each of which has the same likelihood of independently progressing through the multistage process. The model further assumes that this progression of cellular changes must occur in a specific order, though this is not a critical assumption, and that the background, or spontaneous, rate of occurrence of the ith change is a constant λ_i independent of the age of the cell in the absence of any specific carcinogenic insult. If these occurrence rates are small in comparison with the inverse of the life-span, then the background incidence rate of cancer among individuals of age t, $I(t)$, is approximately given by

$$I(t) \alpha \lambda_1 \lambda_2 \cdots \lambda_k (t-w)^{k-1}, \qquad [1]$$

where w is the growth time for a fully transformed cell (i.e., a cell that has undergone all k changes) to become a clinically detectable tumor. The occurrence rates λ_i may be thought of as either rates for spontaneous cellular changes that may occur in the absence of any carcinogenic agents or occurrence rates that are due to a combination of spontaneous change and change induced by environmental "background" carcinogens

Abbreviations used: 2-AAF=2-acetylaminofluorene; BP=benzo[*a*]pyrene; DDT=1,1'-(2,2,2-trichloroethylidene)bis[4-chlorobenzene].

[1] Received May 4, 1979; accepted September 4, 1979.

[2] International Agency for Research on Cancer, 69008 Lyon, France.

[3] Biometry Branch, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare, Bethesda, Md. 20205.

[4] *Address reprint requests to* Dr. Brown *at:* National Cancer Institute, Landow Bldg., Room C508A, Bethesda, Md. 20205.

to which the individual is continuously exposed from birth at a relatively constant level. In this latter situation, the occurrence rates are assumed to be the sum of a spontaneous rate and a carcinogen-induced rate that is a function of the concentration of the background carcinogens at the target cell. In either situation, the occurrence rates are independent of age, and the model in equation [1] is applicable. A number of different multievent theories of the genesis of cancer have been proposed, many of which lead to the mathematical form of the age-specific cancer incidence rate given in equation [1]. Whittemore and Keller (*12*) have reviewed many of these theories and compared some of their consequences with experimental and observational data.

The general mathematical form of the model in equation [1] pertains to the situation in which the occurrence rates of the k changes necessary for cancer expression are constant over the life of the individual. When exposure to an additional carcinogenic stimulus varies with the age of the individual, the mathematical form of the age-specific cancer incidence must be modified. Whittemore (*9*) examined the effect of this additional exposure for the situation in which the occurrence rate of only one of the k necessary changes is affected. Formulas for the excess age-specific cancer incidence $E(t)$, i.e., the incidence above background, are given in "Appendix." In the following discussion, it is assumed that the carcinogenic process consists of at least three stages, though the formulas are not dependent upon the assumption.

When the additional carcinogenic insult begins at age t_0 and continues at a constant level, equation [8] in "Appendix" gives the excess cancer incidence as a function of age. In particular, when the affected stage is the first ($j=1$) or the penultimate ($j=k-1$), the excess incidence at age t is given by

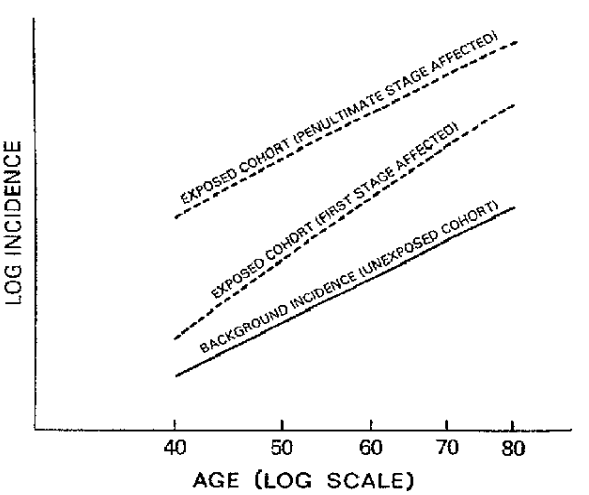
$$\begin{aligned} E(t)\alpha(t-t_0)^{k-1} &= d^{k-1} && j=1, \\ \alpha t^{k-1}-t_0^{k-1} &= (d+t_0)^{k-1}-t_0^{k-1} && j=k-1. \end{aligned} \qquad [2]$$

These relationships indicate that the extra cancer incidence is an increasing function of the exposure duration d for a fixed t_0, no matter which stage is affected (the later the affected stage, the more rapid the increase). In addition, the extra incidence is also an increasing function of the age at which exposure began, t_0, for a fixed duration, except when the affected stage is the first. In terms of excess relative risk (i.e., the excess cancer risk for an exposed individual relative to the cancer risk for an unexposed individual of the same age), this measure is an increasing function of duration of exposure when an early stage is affected and is nearly independent of duration, for moderate durations, when a late stage is affected. A comparison of the age-specific incidence rates between an unexposed cohort for which the incidence is given by equation [1] and a cohort of individuals that have been continuously exposed to an additional carcinogen starting some moderate amount of time since birth (e.g., 15-25 yr of age) can provide an indication of whether the carcinogen affects an early or late stage of the process. The relationship between log incidence and log age will be linear for the unexposed cohort (assuming a negligible tumor growth time w in equation [1]). When the stage affected by the additional carcinogen is the last or penultimate, equations [8] and [2] indicate that the log incidence-log age relationship will be linear or nearly so with the same slope as the unexposed population but at a higher level. However, when the affected stage is the first, since the excess incidence is proportional to a power of exposure duration as opposed to age, the log incidence-log age relationship will be increasing at a more rapid rate than in the unexposed cohort (being similar to the background rate for short durations and becoming more divergent for longer durations). These log incidence-log age relationships are shown graphically in text-figure 1, for which it is assumed that exposure starts at 20 years of age and the carcinogenic process consists of five stages.

When the additional carcinogenic insult begins at age t_0, continues at a constant level for an exposure duration of length d, and then stops, equation [9] in "Appendix" gives the excess cancer incidence for ages after exposure termination. In particular, when the affected stage is the first ($j=1$) or penultimate ($j=k-1$), the excess incidence at age t is given by

$$\begin{aligned} E(t)\alpha(t-t_0)^{k-1}-(t-t_0-d)^{k-1} && j=1, \\ \alpha(t_0+d)^{k-1}-t_0^{k-1} && j=k-1. \end{aligned} \qquad [3]$$

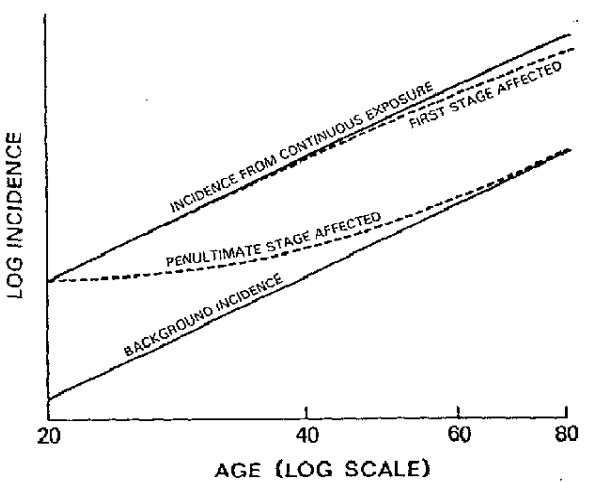
As would be expected, for fixed age-started exposure t_0 and fixed age after exposure stopped t, the excess incidence is an increasing function of exposure duration d, no matter which stage is affected. In addition, these relationships indicate that 1) for fixed duration d and age started t_0, the excess incidence is independent of age after exposure stopped t (when the affected stage is the penultimate $j=k-1$) and is an increasing function of t when $j<k-1$; 2) for fixed duration d and fixed age t, the excess incidence is a decreasing function of age



TEXT-FIGURE 1.—Age-specific cancer incidence for a cohort continuously exposed to a carcinogen from 20 yr of age.

started exposure t_0 (when the affected stage is the first $j=1$) and an increasing function of t_0 when $j=k-1$; and 3) for fixed duration d and fixed time since exposure stopped $r=t-t_0-d$, the excess incidence is independent of the age exposure started t_0 (when the affected stage is the first $j=1$) and an increasing function of age started when $j>1$. Text-figure 2 shows the differential effects of stopping exposure on the age-specific incidence, depending upon which stage of the process is affected by the carcinogenic stimulus. This hypothetical cohort was assumed to have been exposed since birth and to have had exposure stopped at 20 years of age; the number of stages is assumed to be five. When the carcinogen affects the first stage, the incidence after stopping continues to rise for some time almost as sharply as if the exposure had continued. However, when the penultimate stage is affected, the excess incidence is frozen at the age exposure stopped, and the overall incidence rapidly approaches that of the unexposed individuals. A similar pattern occurs when exposure starts at some age beyond infancy.

The excess relative risk increases with increasing duration of exposure for each affected stage other than the last, whereas the effects of age-started exposure and time since exposure stopped depend upon which stage is affected. The excess relative risk decreases with age first exposed when the first stage is affected and increases with age first exposed when the affected stage is the penultimate. In addition, if exposure starts at birth, the excess relative risk decreases with time since exposure stopped no matter which stage is affected. However, if the exposure starts at some age beyond infancy, then the excess relative risk increases, reaches a maximum, and then decreases with time since exposure stopped when the affected stage is the first, and strictly decreases when the penultimate stage is affected. These relationships are shown in text-figures 3A and 3B for each affected stage of a five-stage carcinogenic process with an assumed exposure duration of 5 years. The curves were standardized to be equal to one another at 10 years after exposure stopped (text-fig. 3A) and at 15 years of age (text-fig. 3B). This standardization was done to put each set of curves on a similar scaling to more clearly point out their different behavior.



TEXT-FIGURE 2.—Effect of stopping exposure at 20 yr of age when carcinogenic exposure started at birth. Age-specific incidence.

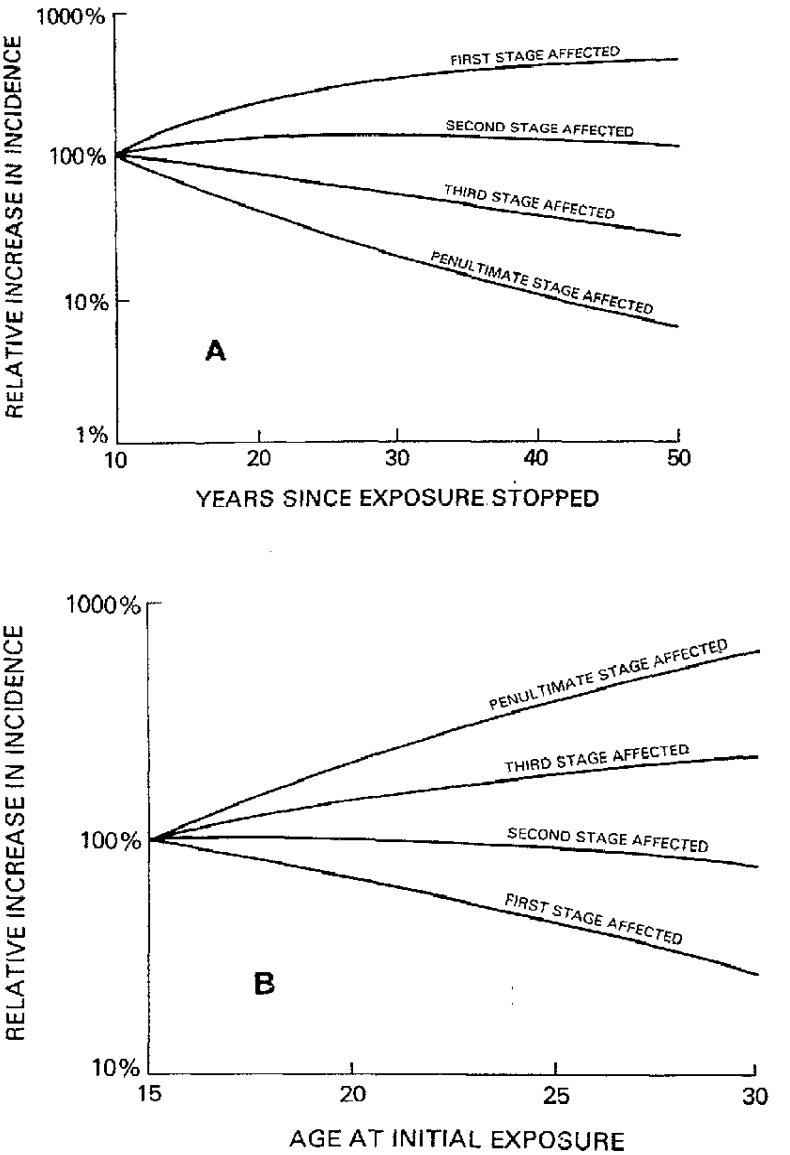
When the additional carcinogenic stimulus affects one or more stages in the process, a general formula equation [10] for the age-specific incidence rate is derived (*see* "Appendix"). In particular, for a constant exposure starting at age t_0 and ending at age t_1, when both the first and penultimate stages are affected by the carcinogen, this excess cancer incidence at age t becomes

$$E(t;1,k-1)\alpha r_1[(t-t_0)^{k-1}-(t-t_1)^{k-1}] + r_{k-1}[t_1^{k-1}-t_0^{k-1}] + r_1 r_{k-1}(t_1-t_0)^{k-1} \qquad t_1 \le t, \qquad [4]$$

where the first term is the excess due to only the first stage being affected, the second term is the excess due to only the penultimate stage being affected, and the last term is that due to both stages being affected. In general, if at least one early stage is affected by the carcinogen, the excess risk will increase with age after the exposure stops. However, if the last stage is also affected, the excess risk may initially drop after exposure termination, due to the cessation of additional risk in individuals who have already undergone $k-1$ of the cellular changes and then start increasing at nearly the same rate as the background but at a higher level, due to the individuals who had undergone the first cellular change before the carcinogenic exposure stopped. An example of this behavior is depicted in text-figure 4 in which the carcinogenic exposure is assumed to start at birth and stop at 40 years of age, and the process is assumed to consist of five stages. Different assumptions concerning the ages exposure started and stopped do not materially change these patterns. Text-figure 4 shows that the magnitude of the effect of stopping exposure will depend upon the relative magnitudes of the carcinogenic effects upon the two affected stages. The example in text-figure 4 assumes that the ratio $r_1:r_k$ is either 4:1 or 1:4. The reduction in cancer incidence due to stopping exposure will be larger when the carcinogenic effect is greater on the last stage than on the first.

EXAMINATION OF DATA

The data we examined came from animal experiments in which a particular treatment was stopped or from epidemiologic situations in which exposure to the carcinogenic agent took place only in a limited and well-defined period of time. Our purpose was to determine whether we could identify qualitative differences in behavior corresponding to that of early- and late-stage carcinogens, i.e., to determine whether the theoretical possibilities predicted by multistage theory occur in practice. By definition, most of the agents we considered are complete carcinogens in the sense that the agent alone induces tumors which otherwise would



TEXT-FIGURE 3.—Excess incidence relative to background for a limited duration exposure. A) Exposure started at 25 yr of age and was of 5-yr duration. Process was five stages. Curves standardized to be equal 10 yr after exposure stopped. B) Exposure duration was 5 yr; current age was 60 yr; process was five stages. Curves standardized to be equal at 15 yr of age.

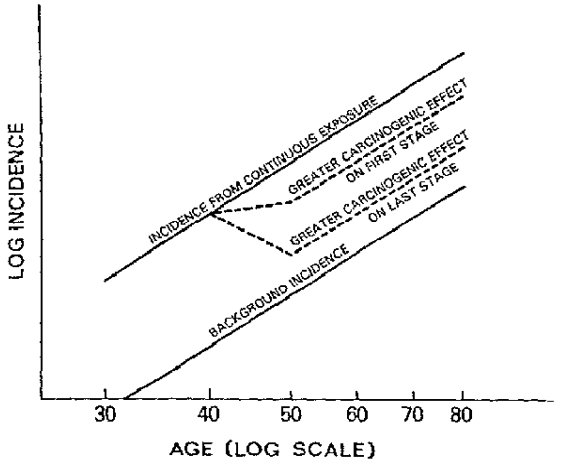
not appear and possibly affects the rate of all the transitions. Our purpose was to determine if agents exert their effect predominantly at early- or late-stage transitions.

Experimental Data

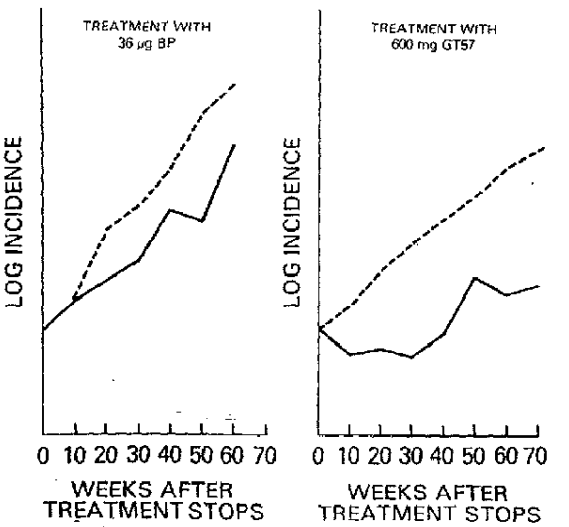
Skin-Painting Experiments

BP and fraction G of T57 cigarette smoke condensate ("GT57") were applied to mouse skin for limited periods of time (table 1). In text-figure 5, we plotted the evolution of the incidence of skin tumors after BP and GT57 treatment was stopped. For each treatment, we graphed two curves that were obtained by summing the observed incidence of new tumor-bearing animals or the incidence expected if the treatment had been continued across the different treatment duration groups. The expected tumor incidence was estimated from a Weibull distribution fitted to the tumor times for all the time periods in which treatment was given. Thus comparing the two curves for each treatment indicates the reduction in tumor incidence achieved by stopping exposure. The background incidence was not included in these plots because it was negligible.

There was a considerably greater reduction in inci-



TEXT-FIGURE 4.—Age-specific incidence after exposure stopped; first and last stages affected. Exposure started at birth and stopped at 40 yr of age.



TEXT-FIGURE 5.—Effect of discontinued treatment on incidence of skin tumors induced by BP and GT57. - - - - = Average expected incidence if treatment continued; ——— = average observed incidence after treatment stopped.

dence for the GT57-treated groups than for the BP-treated groups. For the former, the reduction was immediate; for the latter, the reduction emerged more slowly. Comparing text-figures 4 and 5, we observe that BP appears to act as a carcinogen affecting predominantly an early stage, whereas the tobacco smoke extract behaves more as a late-stage carcinogen.

One would not expect a total contrast in behavior between BP and extract G, because GT57 contains BP and other polynuclear hydrocarbons of similar mutagenic and/or carcinogenic activity. Nevertheless, the difference was marked. BP had a relatively powerful early-stage effect leading to a continuing increase in incidence many weeks after treatment was stopped, whereas extract G appeared to potentiate a weak early-stage effect by a strong later-stage effect. Appreciable reduction in the lifetime cumulative risk could be achieved only if application of BP was stopped early, i.e., 25 weeks, whereas cessation of skin painting with extract G even at 40 weeks reduced the proportion of carcinoma-bearing animals by more than 75% (table 2).

The next two experimental examples concerned feeding experiments and the induction of internal tumors. In both experiments, serial sacrifice of the animals was part of the design, thus giving information on the changing prevalence of tumors with time. As is inevitable, however, with experiments in which tumors of internal organs are induced, precise estimates of age-specific incidence rates were not available.

TABLE 1.—*Design of skin-painting experiments with BP and a fraction of extract from tobacco smoke*[a]

Treatment	Dose/wk	Duration of treatment
GT57	600 mg	0–20 wk
	600 mg	0–30 wk
	600 mg	0–40 wk
	600 mg	Lifetime
BP	36 μg	0–25 wk
	36 μg	0–35 wk
	36 μg	Lifetime

[a] From Whittemore and Keller (*12*) and Lee PN: Unpublished data. Seventy-five mice were used at beginning of expt.

Induction of Liver and Bladder Tumors by 2-AAF in BALB/c Mice

The full experiment has been reported by Littlefield (unpublished data). The experimental groups we considered are listed in table 3. In each group, we counted not only the tumors found when mice were killed on schedule, but also the tumors found among animals that died, or were killed when moribund, before the date scheduled for death. Thus the following figures (reproduced from Littlefield's data) represent the total proportion of animals in the respective groups in which liver or bladder tumors were found. The results for bladder tumors are given in text-figure 6. The effect of removing exposures to 2-AAF was immediate and marked. The proportion of animals found to have bladder tumors was frozen, or nearly frozen, at the level when exposure stopped. The effect of stopping treatment indicates that 2-AAF has a predominant effect on late-stage transitions.

TABLE 2.—*Percentage of animals receiving GT57 or BP and developing tumors or carcinomas*

Treatment	Dose/wk	Duration of painting	Mice with tumors, %	Mice with carcinomas, %
GT57	600 mg	0–20 wk	22.7	2.7
	600 mg	0–30 wk	16.0	2.7
	600 mg	0–40 wk	38.7	5.3
	600 mg	Lifetime	61.3	25.3
BP	36 μg	0–25 wk	60.0	33.3
	36 μg	0–35 wk	68.0	52.0
	36 μg	Lifetime	77.3	68.0

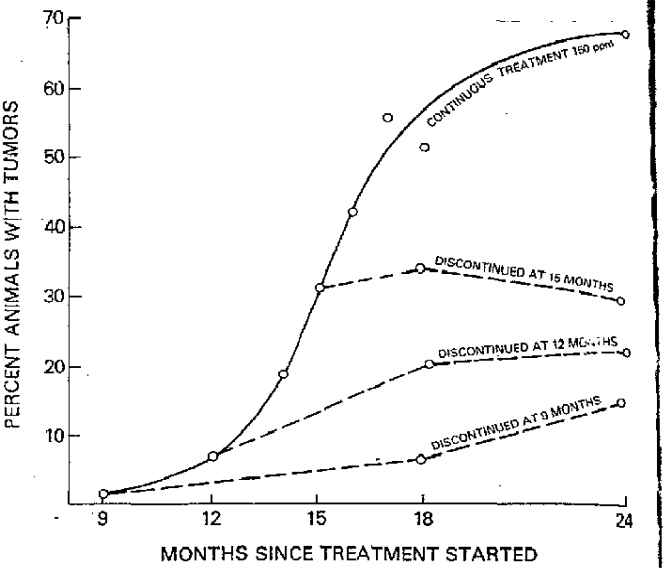
TABLE 3.—*Design for induction of bladder and liver tumors by 2-AAF*[a]

Dose level	Mo of sacrifice:	18	24	18	24	18	24
	Mo on 2-AAF:	15	15	12	12	9	9
		No. of animals/group					
150 ppm		72	72	72	72	72	72
60 ppm		216	216	216	216	216	216

[a] From Littlefield NA: Unpublished data. Discontinued treatment groups included in the present analysis are shown.

For liver tumors, the results were very different (text-fig. 7). Stopping treatment had a relatively minor effect on the subsequent appearance of tumors. There was some slight reduction, but even when treatment stopped at 9 months, the effect was unimpressive. As a carcinogen for the mouse liver, 2-AAF appears to exert its effect predominantly on early-stage transitions.

2-AAF appears to act as an early-stage carcinogen for the liver and as a late-stage carcinogen for the bladder.



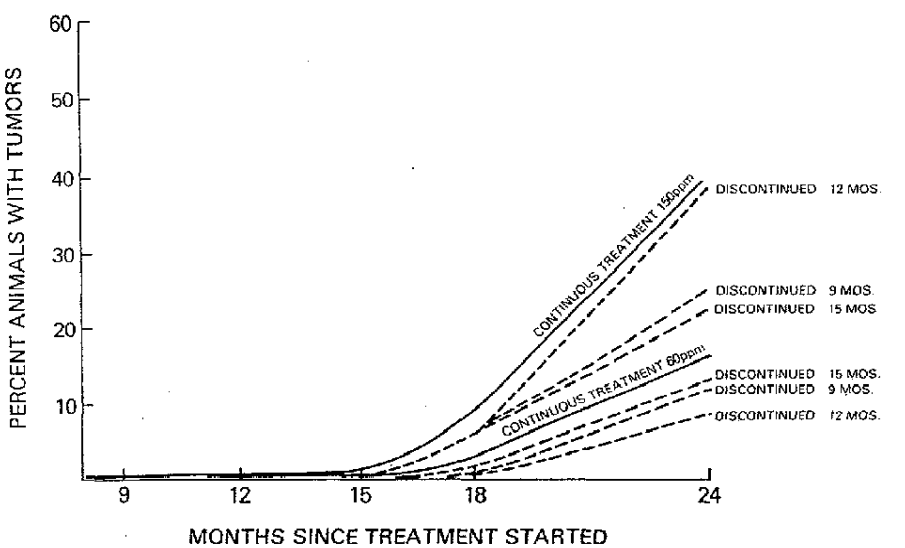
TEXT-FIGURE 6.—Effect of discontinued treatment on incidence of 2-AAF-induced bladder tumors in mice.

Induction of Liver Tumors by DDT in CF1 Mice

The experiment was reported by Tomatis et al. (*13*). The experimental groups we considered are listed in table 4. As with the 2-AAF experiment, the proportions of tumor-bearing animals in each group were calculated, including those dead or killed before the scheduled time for sacrifice. Unlike the two previous sets of data, the present data include an appreciable spontaneous incidence, at least among male mice.

For male mice exposed to DDT for 15 weeks, there was a slight excess of tumors when compared to the spontaneous incidence, but with no indication that the excess over the spontaneous had increased from those killed at 65 weeks to those killed at 120 weeks (table 5). For mice exposed to DDT for 30 weeks, there was a clear excess of tumors when compared to the untreated group, but both the relative and the absolute excess declined with increasing age at which animals were killed. Thus in contrast to treatment with 2-AAF, stopping exposure to DDT appears to freeze the proportion of mice bearing hepatomas, which indicates that the main effect of DDT is on late-stage transitions in the tumorigenic process. Among male CF1 mice treated continuously with 250 ppm DDT, the tumor incidence rose steadily with age (*14*, *15*).

Among female mice (table 4) with very low spontaneous incidence, more tumors were seen among those killed at 95 weeks than at 65 weeks; the group killed at



TEXT-FIGURE 7.—Effect of discontinued treatment on incidence of 2-AAF-induced liver tumors in mice.

TABLE 4.—*Induction of liver tumors by DDT (250 ppm) in CF1 mice*[a]

	Killed at wk:								
	65			95			120		
Wk of treatment	0	0–15	0–30	0	0–15	0–30	0	0–15	0–30
Males[b]	70 (12)	60 (13)	60 (38)	83 (24)	60 (25)	60 (41)	98 (33)	60 (25)	60 (37)
Females[b]	69 (0)	60 (3)	54 (4)	72 (0)	60 (11)	55 (11)	90 (1)	60 (5)	54 (11)

[a] From Tomatis et al. (*13*). Treatment groups considered in present series are shown.
[b] No. of animals killed or that died in the interval; No. of mice with hepatomas at or before death are in *parentheses*.

120 weeks did not show any further increase. The numbers were too small to modify substantially the conclusion drawn from the data on the effect of DDT on male mice, except perhaps to suggest a slight early-stage effect among the females.

Exposure to DDT does not necessarily stop when administration ceases, because DDT is stored in many organs at substantial levels. However, because the effect of stopping administration appears to be a rapid reduction in the rate of late-stage transition, the residual effect of the stored DDT cannot be large. There would be greater ambiguity if an early stage had been predominantly affected (*see* "Asbestos" below).

The mouse data we have presented demonstrate that for two organs, the liver and the skin, we can affect predominantly either early- or late-stage transitions, depending on the agent used, and that a single compound (2-AAF) can apparently affect different stages in different organs. The data on DDT show a carcinogen that has been demonstrated to be only weakly mutagenic, affecting late stages in the process (*16*).

Epidemiologic Data

Cigarette Smoking and Risk for Lung Cancer

Among continuing cigarette smokers, lung cancer incidence rises as approximately the fourth power of duration of smoking (*5*), which indicates that, in terms of multistage theory, cigarette smoke has a strong effect on an early-stage transition. If only late-stage transition were affected, we would expect to see the age-specific incidence rise almost in parallel to that of nonsmokers, but at a higher level. However, among those who stop smoking, the age-adjusted relative risk begins to fall within a few years (*17*). In table 6, we show the mortality rate among ex-smokers as a proportion of the rate expected if they had continued smoking and also as a proportion of the rate among nonsmokers of the same age. The fall in incidence is close to that expected on removal of a penultimate-stage carcinogen (text-fig. 2). The mortality rate remains roughly constant at the level reached when smoking stopped. Thus both an early and a late stage appear to be affected, with cigarette smoking affecting later-stage transition rates to a greater degree than the early-stage rates. One might expect that if more than one stage is affected, the increase in risk with dose might be more than linear. When attention is restricted to individuals with a record of unchanging smoking habits and who smoke only cigarettes, then the dose response appears nearly quadratic (*7*).

TABLE 5.—*Excess incidence in male mice treated with DDT for limited periods, as compared to incidence in untreated animals*[a]

Group killed at	Duration of treatment			
	0–15 wk		0–30 wk	
	Relative risk	Absolute excess, %	Relative risk	Absolute excess, %
65 wk	1.26	4.5	3.69	46.2
95 wk	1.44	12.8	2.36	39.4
120 wk	1.24	8.0	1.83	28.0

[a] Treatment groups as listed in table 4.

Radiation

We considered cancers other than leukemia, because the multistage models we have described do not accord with the epidemiologic behavior of leukemia (*6*).

Table 7, column A gives the relative risk of mortality from all cancers other than leukemia among survivors of the atomic bomb explosion in Japan (*18*) as a function of time since the explosion. The values given are the risks among those exposed at 100 rads or more relative to the risks among those exposed to 0–9 rads. Thirty years after the bomb, the relative risk appears to be still rising.

Table 7, column B gives the relative risk of developing breast cancer among Japanese women exposed to the atomic bomb explosions (*19*).

Table 7, columns C and D show the risk for breast

TABLE 6.—*Evolution of mortality from lung cancer among ex-cigarette smokers*[a]

Measurement	Yr since smoking stopped				
	0	<5	5–9	11–14	>15
No. of deaths among ex-smokers[b]		10	12	8	7
No. of deaths as percent of No. expected among continuing smokers	100	68	35	25	11
No. of deaths divided by No. expected among lifelong nonsmokers	15.8	10.7	5.9	4.7	2.0

[a] From Doll and Peto (*17*).
[b] Excluding those who stopped smoking after developing lung cancer.

TABLE 7.—*Evolution of relative risk following limited exposure to radiation*[a]

A Atomic bomb survivors with cancers other than leukemia[b]		B Atomic bomb survivors with breast cancer[c]		C Breast cancer after repeated chest fluoroscopies[d]		D Breast cancer after irradiation for postpartum mastitis[e]		E Irradiation for ankylosing spondylitis: Heavily exposed sites other than leukemia[f]		F Irradiation for metropathia hemorrhagica: Heavily irradiated sites[g]	
Time since exposure, yr	Relative risk	Time since exposure, yr	Relative risk	Time since first exposure, yr	Relative risk	Time since first exposure, yr	Relative risk	Time since first exposure, yr	Relative risk	Time since exposure, yr	Relative risk
5–9	1.4 (29)	5–9	4.0 (5)	0–4	1.1 (1)	0–9	1.0 (1)	0–2	1.4	0–4	0.3 (2)
10–13	1.0 (18)	10–14	2.4 (6)	5–9	1.3 (2)	10–19	1.5 (14)	3–5	1.3 (27)	5–9	1.6 (15)
14–17	1.4 (33)	15–19	2.4 (11)	10–14	0.8 (2)	20–34	3.4 (22)	6–8	1.2 (21)	10–14	1.6 (17)
18–21	1.1 (34)	20–24	4.9 (12)	15–19	1.4 (5)			9–11	1.9 (45)	15–19	1.4 (14)
22–25	1.3 (40)			20–24	2.4 (11)			12–14	1.7 (46)	20–24	1.3 (9)
26–29	1.5 (45)			25–29	1.8 (8)			15–17	1.6 (43)	25–29	1.4 (4)
				30–34	1.7 (6)			18–20	1.5 (26)		
				35+	2.7 (6)			21–23	1.3 (11)		
								24–26	0.9 (4)		

[a] No. of cases are in *parentheses*.
[b] Mortality. Relative risk of those exposed to 100+ rads to those exposed to 0–9 rads. From Beebe et al. (*18*).
[c] Morbidity. Relative risk of those exposed to 100+ rads to those exposed to 0–9 rads. From McGregor et al. (*19*).
[d] From Boice and Monson (*20*).
[e] From Shore et al. (*21*).
[f] From Smith and Doll (*22*).
[g] From Smith and Doll (*23*).

cancer following irradiation for tuberculosis (*20*) and for postpartum mastitis (*21*), respectively. The relative risk appears to reach a plateau after about 20 years, with no signs of diminishing 30 or more years after exposure.

Table 7, column E displays the evolution of risk for heavily exposed sites following irradiation for ankylosing spondylitis (*22*). Unlike the previous two examples, the risk appears to decrease 10 years after exposure, but the decrease is not statistically significant.

Table 7, column F gives the corresponding data for women irradiated for metropathia hemorrhagica (*23*). A slight decline in the relative risk 15 years and more after irradiation is again apparent, but the decline is not statistically significant. Taken together, the results given in table 7 indicate that the relative risk for neoplasia at exposed sites, leukemia excepted, rises to an apparent plateau about 15 years after exposure and remains high for 30 years or more after exposure.

A further example is provided by the experience of children irradiated in infancy. The consequent risk for thyroid cancer is so high and the expected number of cases among the unexposed population so low that the relative risk is perhaps an inappropriate measure, but the absolute risk is increasing at 35 years of age and over (*24*), although the numbers are small.

In terms of multistage theory, the observed behavior would occur if irradiation were to provoke a burst of early-stage transitions. The fact that radiation carcinogenesis may follow different pathways from chemical carcinogenesis does not prevent one from attempting to describe it in terms of the same formal multistage model.

Asbestos

Asbestos is associated with several types of tumors. We considered the two for which the data are most extensive, mesothelioma and bronchogenic carcinoma.

Seidman et al. (*25*) have reported on a group of workers exposed to asbestos for a short time during the Second World War. We restricted our attention to those employed for less than 2 years and considered the 5-year increments in the difference between the observed cumulative probability of death due to lung cancer and the expected cumulative probability (table 8).

Notwithstanding the irregularities caused by small numbers, there is a clearly increasing increment in the excess cumulative probability. The increments will approximate closely the actual incidence during the relevant time period, so that table 8 indicates an increasing excess incidence similar to that shown in

TABLE 8.—*Percentage increment in the excess cumulative probability of lung cancer*[a]

Length of exposure, mo	Yr since first exposure				
	5–9	10–14	15–29	20–24	25–30
<1	−0.15	−0.24	−0.35	1.09	2.67
1	−0.21	0.74	2.74	−0.51	0.47
2	−0.27	−0.38	0.69	1.89	4.20
3–5	−0.24	−0.34	0.91	1.51	0.11
6–11	−0.29	0.47	1.83	2.43	0.20
12–23	−0.13	2.24	1.33	1.21	2.80
Average increment	−0.215	0.415	1.192	1.270	1.742

[a] Difference between observed and expected cumulative probabilities. From Seidman et al. (*25*).

text-figure 2 for short-term exposure to an early-stage carcinogen.

However, with asbestos there is some ambiguity in interpreting the evolution of risk after the external exposure has stopped, because asbestos bodies remain in the lungs. It might be more appropriate to consider exposure as being continuous but at a decreasing level as the asbestos bodies are either excreted or their carcinogenic ability is reduced. However, the mechanism of action of asbestos carcinogenesis is unknown, and it is not clear that its carcinogenic effect remains with the asbestos bodies that remain in the lungs. The observed increasing excess cancer incidence is thus consistent either with an early-stage effect or with a late-stage effect resulting from the asbestos remaining in the lungs.

Data on mesothelioma are not reported from the cohort just described. Table 9 gives data on the follow-up of a cohort reported by Newhouse and Berry (*26*). Most of the cohort had been exposed for less than 2 years, and half of the mesotheliomas developed among this group. Evolution of risk, however, is not given separately for those exposed for a short duration.

However, the quadratic residence time model as described by Peto (*27, 28*) appears to fit the observed data reasonably well. Under this model, the incidence at times T, e.g., $I(T)$, is proportional to $\int_0^T (T-t)^2 c(t)dt$, where $c(t)$ is the exposure level at time t. It should be noted that this quadratic residence time model is mathematically equivalent to a model derived from the assumption of a first-stage effect in a four-stage carcinogenic process. As with the risk for lung cancer following asbestos exposure, we can interpret these data as describing either the effect of a continuous exposure due to the inhaled fibers or the effect of short-term exposure to an early-stage carcinogen.

Nickel

We considered the cohort of workers from the South Wales nickel refinery studied by Doll and his coworkers (*29–31*). Tumors of both the lung and the nasal sinuses were associated with exposure before 1930, but because the evolution of lung cancer risk since that time may well have been affected by differential mortality among heavy cigarette smokers (*30*), we considered only the changing risk for cancer of the nasal sinuses. No excess risk for tumors of either the lung or the nasal sinuses has been observed among people first exposed after 1930. Changes also occurred in the operations at the refinery at this time, which it is assumed reduced the carcinogenic exposure to inappreciable levels. Risk varied with both age at and year of first employment. After standardizing for these two factors, the incidence of nasal sinus tumors among men employed before 1924 was relatively constant from 1939 to 1966 (table 10), i.e., 9–36 years after exposure was thought to have stopped. The spontaneous incidence in the population was low enough to be ignored. The effect of cessation of exposure is as if a late stage had been affected. As with cigarette smoking, other stages may be affected as well, but the predominant effect on the evolution of incidence after exposure has stopped appears to come from the effect on a late stage.

TABLE 9.—*Mesothelioma mortality rates following exposure to asbestos*[a]

Time since first exposure, yr	Rate per 10^5 person-years[b]
10–14	6 (1)
15–19	45 (6)
20–24	152 (15)
25–29	171 (11)
30+	318 (12)

[a] From Newhouse and Berry (*26*).
[b] No. of cases are *in parentheses*.

TABLE 10.—*Number of men developing nasal sinus cancer by calendar year of observation and number expected after standardization for year and age at first employment*[a]

Calendar yr of observation	No. of nasal sinus cancers		No. observed/ No. expected
	Observed	Expected[b]	
1939–41	7	3.63	1.93
1942–46	8	7.28	1.10
1947–51	9	9.66	0.93
1952–56	5	9.34	0.54
1957–61	6	6.28	0.96
1962–66	5	3.82	1.31
All yr	40	40.01	
χ^2 for trend = 0.95, df = 1, $P > 0.30$			

[a] From Doll et al. (*30*).
[b] The expected numbers are not based on population incidence data but were obtained from the observed cases by assuming that the incidence was proportional to the man-yr at risk after standardizing for calendar yr and age at first employment. The uniformity of the observed to expected ratio thus reflects a constancy over follow-up time of the absolute rather than relative excess risk.

Occupational Bladder Cancer

A variety of occupations increase the risk for bladder cancer, and in many of them the active carcinogen is not known. Furthermore, for situations in which specific carcinogens have been identified and eliminated, e.g., the aromatic amines in the dye industry and the rubber industry, it is not known if other carcinogens are also present. Thus the finding that bladder cancer mortality in the rubber industry in the United Kingdom was still elevated in 1972–74, more than 20 years after the banning of α- and β-naphthylamine and of benzidine (*32*) may well be due to other carcinogens rather than the clinical surfacing of early-stage events induced by the eliminated known carcinogens.

Hoover and Cole (*33*), however, report on the risk of men who had been employed for less than 10 years in an occupation classified as hazardous for bladder cancer (table 11). The data came from a case-control study, and an occupation was classified as hazardous if either there was an observed increased risk or the occupation was known from previous studies to increase risk (*34*).

TABLE 11.—*Relative risk for bladder cancer following occupational exposure*[a]

Duration of work in hazardous occupation ≤10 yr	No. of persons never employed	Interval since first employment, yr		
		≤40	41–55	56+
No. of cases	217	16	19	17
No. of controls	277	13	10	5
Relative risk		1.6	2.4	4.3

[a] From Hoover and Cole (*33*).

Although the upward trend in risk does not achieve statistical significance, the data are clearly incompatible with much of a downward trend. As bladder cancer in the general population in the United States increases at the fourth or fifth power of age, even a constant relative risk in table 11 would correspond to a rapid increase in the excess risk. The data thus suggest that the predominant action of the carcinogens to which this group were occupationally exposed is to affect early-stage transitions.

AGE AT FIRST EXPOSURE

We have concentrated here on the different ways in which risk evolves following cessation of exposure, depending on whether early or late stages are affected. As we indicated previously, the relationship between age at first exposure and subsequent risk should also depend on the stage affected. Among asbestos-exposed workers followed by Selikoff et al. (*35*) and among those exposed to industrial bladder carcinogens (*33*), the relative risk is higher the younger the age at first exposure, as expected if they are early-stage carcinogens. For cigarette smoking, variation in the age at starting to smoke is insufficient to determine if and how the excess risk might change. The effect of age at irradiation on subsequent risk depends on the site at risk. For breast cancer, variation in excess risk may reflect the developmental state of the tissue at exposure, being highest in the 10–19-year age group and particularly high just preceding menarche (*36*). In the two studies by Doll discussed earlier (*22, 23*), which were based on a collection of different sites, the relative risk was constant over different ages at exposure, which indicates a possible combination of early- and late-stage effects (*see* text-fig. 3B). One might speculate that the excess incidence within 15–20 years of exposure, the data on which the constancy of relative risk with age at exposure is based, results from these combined effects, whereas the continuation of the excess risk more than 30 years after exposure could correspond to the early-stage effects. After standardizing for exposure duration, the excess incidence of nasal sinus tumors among nickel workers increases with age at first exposure (*30*), which is consistent with our previous interpretation that a late stage is implicated.

DISCUSSION

Our concern has been to investigate the effect of reduction in levels of carcinogenic exposure on future risk. Future risk, the long-term effect of limited exposure, is of prime importance when assessing the need for intervention. In a cost-benefit analysis, the long-term costs should figure highly. Multistage models predict that the effect may vary widely, in some situations the incidence evolving almost as if exposure had not been reduced, in others the excess incidence remaining constant or even declining. The differences in behavior correspond to whether early- or late-stage transitions are being predominantly affected. The experimental data that we considered demonstrated clearly that these two types of behavior occur. The risk of liver tumors among mice treated with 2-AAF or of skin tumors among mice skin-painted with BP increases after treatment has been discontinued at nearly the same rate as that among mice continuously treated. By contrast, the risk for bladder tumors induced by 2-AAF, for liver tumors induced by DDT, or for skin tumors induced by an extract of stale tobacco smoke condensate diverges sharply from the risk among continuously treated animals. These examples suggest that the effect of discontinuing treatment is not a property of the organ involved, or even of the chemical, but appears specific for the organ-chemical pair. However, surprisingly few experiments seem to have given adequate information on tumor incidence following cessation of exposure. Further experimentation in this direction should clearly be done to clarify the predominant patterns of behavior. It might also indicate how one could expect different classes of compound to act and identify other biologic activities as predictors of the stage at which a substance predominantly acts. Mutagenicity may be an indication of early-stage carcinogenicity, for example.

Among humans, the effect of stopping exposure will depend not only on the effect which that exposure has on each of the transition rates, but also on the other environmental carcinogens to which we are exposed. The effect will depend on the proportional contribution made to each of the transition rates by the exposure of interest. There are, nevertheless, the same two basic patterns of behavior as exemplified on the one hand by radiation and asbestos, with early-stage transitions predominantly affected, and on the other by cigarette smoking and nickel, with late-stage transitions affected. Additional examples could be given for each of the two patterns. Migrant studies indicate that the risk for gastric cancer is set in the first 20 years of life (*37*) with the incidence evolving as the fourth power of age thereafter. The use of conjugated estrogens to palliate menopausal symptoms appears to cause a rapid increase in risk for endometrial cancer. The recent decline in rates for this tumor, which previously had been rising, possibly reflects a rapid decrease in risk following cessation of exposure, consistent with late-stage action (*38*).

The consequences of these two types of behavior are of importance when considering intervention or control strategies. Without additional information on the nature of the exposure, there seems no ground for

TABLE 12.—*Comparison of effects of early- and late-stage carcinogens on excess lifetime cancer risk over background*[a]

Age exposure starts: Affected stage:	At birth		At age 20 yr		At age 40 yr	
	First	Penultimate	First	Penultimate	First	Penultimate
Duration of exposure, yr						
2	12	<1	15	1	20	4
5	28	<1	35	2	44	11
10	50	<1	58	6	71	25
20	77	2	85	19	94	54
30	90	8	96	39	99	79
40	97	21	99	62	>99	94
Lifetime	100	100	100	100	100	100

[a] Expressed as percent of excess for lifetime exposure (110 yr) conditional on cancer-free survival until start of exposure. Five-stage carcinogenic process was assumed. Background risk from birth was assumed to be 0.01. Excess due to lifetime exposure from birth was assumed to be 0.04. Competing risks from other mortality are from U.S. Lifetables (196971, white males).

sanguinely believing that the effect of removing exposure would always be as immediate as the effect of stopping smoking, because the elimination of predominantly early-stage carcinogens from the environment would only slowly reduce the future cancer burden. In terms of immediate intervention, the most useful progress seems to lie in identifying environmental agents that predominantly accelerate late-stage transitions. For control purposes, the long-term hazards associated with early-stage carcinogens may pose the greatest problem. As predicted from the multistage model, we give in table 12 the lifetime risk associated with exposures of varying duration compared with the lifetime risk associated with lifetime exposure. Between 5 and 10 years of exposure to an early-stage carcinogen are sufficient to generate nearly half of the risk of lifetime exposure. Control strategies that depend on the availability of human evidence are clearly inadequate to prevent the long-term hazards consequent to the introduction of an early-stage carcinogen into the environment. Control measures will have to be based on carcinogenicity tests in other species and on short-term assays. Experimentation that facilitates the identification of early-stage carcinogens needs to be encouraged.

APPENDIX

We give here some general mathematical relationships between age and cancer incidence based on a multistage theory of carcinogenesis. The theoretical assumptions leading to these relationships are discussed by Armitage and Doll (*11*) and Peto (*6*). This theory assumes that the carcinogenic process consists of k cellular changes that have occurrence rates consisting of the sum of a background rate λ_i independent of age and a carcinogen-induced rate $\lambda'_i c(t)$ that is proportional to the concentration $c(t)$ of the additional carcinogenic exposure at time t:

$$\lambda_i^*(t)=\lambda_i+\lambda'_i c(t),\ i=1,\cdots,k. \qquad [5]$$

Whittemore and Keller (*12*) have shown that the probability of an individual's having a specific cell that has undergone k-1 changes by age t is approximately given by

$$P_{k-1}(t)\alpha\int_0^t \lambda_{k-1}^*(x_{k-1})\int_0^{x_{k-1}}\lambda_{k-2}^*(x_{k-2})\cdots\int_0^{x_2}\lambda_1^*(x_1)dx_1\cdots dx_{k-1}. \qquad [6]$$

Thus the age-specific incidence rate of cancer occurrence is reasonably approximated by

$$I^*(t)\ \alpha\ \lambda_k^*(t-w)P_{k-1}(t-w), \qquad [7]$$

where w is the tumor growth time as in equation [1].

To derive the age-specific incidence rate for an individual exposed to an additional carcinogenic exposure for a limited duration, we assume that the additional exposure is at a constant level, begins at age t_0, ends at age t_1, and increases the cellular event rates to $\lambda_i+\lambda'_i$. We also assume that the tumor growth time is negligible. Thus the incidence rate can be thought of as a sum of terms for which the first $i-1$ events occur before the additional exposure, the next $j-1$ events occur during the exposure period, and the last $k-i-j+1$ events occur after the exposure stops. The probability that a specific cell has undergone $k-1$ changes by time t is then given by the sum

$$P_{k-1}(t)=\sum_{i=1}^{k}\sum_{j=1}^{k-i+1}P_{k-1}^{(i,j)}(t),$$

where

$$P_{k-1}^{(i,j)}(t)\alpha\left[\int_{t_1}^{t}\lambda_{k-1}\int_{t_1}^{x_{k-1}}\lambda_{k-2}\cdots\int_{t_1}^{x_{i+j}}\lambda_{i+j-1}dx_{i+j-1}\cdots dx_{k-1}\right]$$
$$\times\left[\int_{t_0}^{t_1}(\lambda_{i+j-2}+\lambda'_{i+j-2})\int_{t_0}^{x_{i+j-2}}(\lambda_{i+j-3}+\lambda'_{i+j-3})\cdots\int_{t_0}^{x_{i+1}}(\lambda_i+\lambda'_i)dx_i\cdots dx_{i+j-2}\right]$$
$$\times\left[\int_0^{t_0}\lambda_{i-1}\int_0^{x_{i-1}}\lambda_{i-2}\cdots\int_0^{x_2}\lambda_1 dx_1\cdots dx_{i-1}\right]$$

Therefore, the age-specific occurrence rate of the kth change $\lambda_k P_{k-1}(t)$ is given by

$$I(t)\alpha \sum_{i=1}^{k}\sum_{j=1}^{k-i+1}\left[\prod_{p=i+j-1}^{k}\lambda_p\right]\frac{(t-t_1)^{k-i-j+1}}{(k-i-j+1)!}\left[\prod_{q=i}^{i+j-2}(\lambda_q+\lambda'_q)\right]$$

$$\times\frac{(t_1-t_0)^{j-1}}{(j-1)!}\left[\prod_{r=1}^{i-1}\lambda_r\right]\frac{t_0^{i-1}}{(i-1)!} \qquad t_1\le t.$$

When exposure has not ended by age t, i.e., $t_0\le t<t_1$, the age-specific occurrence rate is a special case of the above, where t_1 is set equal to t (and thus j must be equal to $k-i+1$):

$$I(t)=(\lambda_k+\lambda'_k)P_{k-1}(t)$$

$$\alpha\sum_{i=1}^{k}\left[\prod_{p=i}^{k}(\lambda_p+\lambda'_p)\right]\frac{(t-t_0)^{k-i}}{(k-i)!}\left[\prod_{q=1}^{i-1}\lambda_q\right]\frac{t_0^{i-1}}{(i-1)!}$$

$$t_0\le t<t_1.$$

The excess cancer incidence $E(t)$ (i.e., the difference between the total incidence $I^*(t)$ in equation [7] and the background incidence $I(t)$ in equation [1]) can be written as

$$E(t)\alpha\sum_{i=1}^{k}\sum_{j=1}^{k-i+1}\left[\prod_{p=i}^{i+j-2}(1+r_p)-1\right]$$

$$\times\frac{(t-t_1)^{k-i-j+1}(t_1-t_0)^{j-1}t_0^{i-1}}{(k-i-j+1)!\,(j-1)!\,(i-1)!} \qquad t_1\le t,$$

where $r_p=\lambda'_p/\lambda_p$.

Whittemore (9) has derived the following simplified expressions for the excess cancer incidence if only one of the k cellular changes is affected by the additional carcinogenic exposure. When the additional exposure begins at age t_0 and continues at a constant level, the excess cancer incidence rate at age t is given by

$$E(t)\alpha\begin{cases}\displaystyle\int_0^{t-t_0}(t-t_0-x)^{k-1-j}(t_0+x)^{j-1}dx & j<k,\\ \alpha t^k & j=k,\end{cases} \qquad [8]$$

where k represents the number of cellular changes, or stages, necessary for cancer expression, j represents the stage affected by the additional exposure, and the tumor growth time w is assumed to be negligible.

When this additional exposure is of a limited duration d, then the excess incidence rate at age t after the exposure has stopped ($t>t_0+d$) is given by

$$E(t)\alpha\int_0^{d}(t-t_0-x)^{k-1-j}(t_0+x)^{j-1}dx \quad j<k. \qquad [9]$$

If the single affected stage is the last, $j=k$, then the excess incidence is zero for any age beyond termination of the exposure (this of course assumes that the time from occurrence of the last cellular change until clinical detection is negligible).

When more than one stage of the carcinogenic process is affected by the additional carcinogen, this excess incidence can be factored into a sum of terms that represent the excess risk due to each affected stage alone and all combinations of jointly affected stages. The case of two affected stages, I and J ($>I$), is particularly straightforward. To simplify the notation, we shall let

$$S(i,j)=\frac{(t-t_1)^{k-i-j+1}(t_1-t_0)^{j-1}t_0^{i-1}}{(k-i-j+1)!\,(j-1)!\,(i-1)!}.$$

Then the nonzero terms that contribute to the summation for excess risk are

$$E(t)\alpha r_I\sum_{i=1}^{I}\sum_{j=I-i+2}^{J-i+1}S(i,j)+r_J\sum_{i=I+1}^{J}\sum_{j=J-i+2}^{k-i+1}S(i,j)$$

$$+(r_Ir_J+r_Ir_Jr_IJ)\sum_{i=1}^{I}\sum_{j=J-i+2}^{k-i+1}S(i,j),$$

which can be rewritten as

$$E(t)\alpha r_I\sum_{i=1}^{I}\sum_{j=I-i+2}^{k-i+1}S(i,j)+r_J\sum_{i=1}^{J}\sum_{j=J-i+2}^{k-i+1}S(i,j)$$

$$+r_Ir_J\sum_{i=1}^{I}\sum_{j=J-i+2}^{k-i+1}S(i,j), \qquad [10]$$

where the first term is the excess risk that would be obtained if only the Ith stage was affected by the carcinogenic exposure, the second term is the excess risk if only the Jth stage was affected, and the third term is the excess risk if both stages were required to be affected. The case of more than two affected stages follows by analogy. Thus the overall effect of a carcinogen that increases the rates of two or more cellular changes can be thought of as consisting of its effect on each separate stage plus its effect on all combinations of jointly affected stages.

REFERENCES

(1) Cook PJ, Doll R, Fellingham SA. A mathematical model for the age distribution of cancer in man. Int J Cancer 1969;4:93-112.

(2) Lee PN, O'Neill JA. The effect of both time and dose applied on tumour incidence rates in benzpyrene skin painting experiments. Br J Cancer 1971;25:759-771.

(3) Berry G, Wagner JC. The application of a mathematical model describing the times of occurrence of mesotheliomas in rats following inoculation with asbestos. Br J Cancer 1969;23: 582-586.

(4) Peto R, Roe FJ, Lee PN, Levy L, Clack J. Cancer and aging in mice and men. Br J Cancer 1975;32:422-426.

(5) Doll R. The age distribution of cancer. Implications for models of carcinogenesis. J R Stat Soc A 1971;134:133-155.

(6) Peto R. Epidemiology, multi-stage models and short term mutagenicity tests. In: Hiatt HH, Watson JD, Winsten JA,

eds. Origins of human cancer. Vol 4. New York: Cold Spring Harbor Laboratory, 1977:1403–1428.

(7) DOLL R, PETO R. Cigarette smoking and bronchial carcinoma: Dose and time relationships among regular smokers and lifelong non-smokers. J Epidemiol Community Health 1978;32: 303–313.

(8) HAMILTON MA, HOEL DG. Detection of synergistic effects in carcinogenesis. Biometrics 1980. In press.

(9) WHITTEMORE AS. Epidemiologic implications of the multistage theory of carcinogenesis. In: Whittemore AS, ed. Environmental health quantitative methods. Philadelphia: Society for Industrial and Applied Mathematics, 1977:72–87.

(10) WHITTEMORE AS. The age distribution of human cancers for carcinogenic exposures of varying intensity. Am J Epidemiol 1977;106:418–432.

(11) ARMITAGE P, DOLL R. Stochastic models for carcinogenesis. In: Neyman J, ed. Proceedings of the fourth Berkeley symposium on mathematical statistics and probability. Vol 4. Berkeley and Los Angeles: Univ California Press, 1961:19–38.

(12) WHITTEMORE AS, KELLER JB. Quantitative theories of carcinogenesis. Society for Industrial and Applied Mathematics Review 1978;20:1–30.

(13) TOMATIS L, TURUSOV V, CHARLES RT, BOIOCCHI M, GATI E. Liver tumors in CF-1 mice exposed for limited periods to technical DDT. Z Krebsforsch 1974;82:25–35.

(14) TOMATIS L, TURUSOV V, DAY N, CHARLES RT. The effect of long-term exposure to DDT on CF-1 mice. Int J Cancer 1972; 10:489–506.

(15) TURUSOV VS, DAY NE, TOMATIS L, GATI E, CHARLES RT. Tumors in CF-1 mice exposed for six consecutive generations to DDT. J Natl Cancer Inst 1973;51:983–997.

(16) PLANCHE G, CROISY A, MALAVEILLE C, TOMATIS L, BARTSCH H. Metabolic and mutagenicity studies on DDT and 15 derivatives. Detection of 1,1-bis(p-chlorophenyl)-2,2-dichloroethane and 1,1-bis(p-chlorophenyl)-2,2,2-trichloroethyl acetate (kelthane acetate) as mutagens in *Salmonella typhimurium* and of 1,1-bis(p-chlorophenyl)-ethylene oxide, a likely metabolite, as an alkylating agent. Chem Biol Interact 1980. In press.

(17) DOLL R, PETO R. Mortality in relation to smoking: 20 years' observation on male British doctors. Br Med J 1976;2:1525–1536.

(18) BEEBE GW, KATO H, LAND CE. Mortality experience of atomic bomb survivors 1950–74. Life Span Study Report 8. Radiation Effects Research Foundation Technical Report TR 1-77, 1977.

(19) MCGREGOR DH, LAND CE, CHOI K, et al. Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki 1950–69. J Natl Cancer Inst 1977;59:799–811.

(20) BOICE JD, MONSON RR. Breast cancer in women after repeated fluoroscopic examinations of the chest. J Natl Cancer Inst 1977;59:823–832.

(21) SHORE RE, HEMPELMANN LH, KOWALUK E, et al. Breast neoplasms in women treated with X-rays for acute post partum mastitis. J Natl Cancer Inst 1977;59:813–822.

(22) SMITH PG, DOLL R. Age and time dependent changes in the rates of radiation induced cancers in patients with ankylosing spondylitis following a single course of X-ray treatment. In: International Atomic Energy Agency symposium on the late biological effects of ionizing radiation, Vienna, March 13–17, 1978. Vienna: International Atomic Energy Agency, 1978:205–214.

(23) ———. Late effects of X-irradiation in patients treated for metropathia haemorrhagica. Br J Radiol 1976;49:224–232.

(24) HEMPELMANN LH, HALL WJ, PHILLIPS M, COOPER RA, AMES WR. Neoplasms in persons treated with X-rays in infancy. Fourth survey in 20 years. J Natl Cancer Inst 1975;50:519–530.

(25) SEIDMAN H, LILIE R, SELIKOFF IJ. Short term asbestos exposure and delayed cancer risk. In: Nieburgs HE, ed. Prevention and detection of cancer. Part I. Prevention. New York: Marcel Dekker, 1977:943–960.

(26) NEWHOUSE ML, BERRY G. Prediction of mortality from mesothelial tumors in asbestos factory workers. Br J Ind Med 1976; 33:147–151.

(27) PETO J. The hygiene standard for chrysotile asbestos. Lancet 1978;1:484–489.

(28) ———. Dose response relationships for asbestos related disease: Implications for hygiene standards. II. Mortality. Ann NY Acad Sci 1979. In press.

(29) DOLL R. Cancer of the lung and nose in nickel workers. Br J Ind Med 1958;15:217–223.

(30) DOLL R, MORGAN LG, SPEIGER FE. Cancers of the lung and nasal sinuses in nickel workers. Br J Cancer 1970;24:623–632.

(31) DOLL R, MATHEWS JD, MORGAN LG. Cancer of the lung and nasal sinuses in nickel workers: A reassessment of the period of risk. Br J Ind Med 1977;34:102–105.

(32) FOX AJ, COLLIER PF. A survey of occupational cancer in the rubber and cable making industries: Analysis of deaths occurring in 1972–74. Br J Ind Med 1976;33:249–264.

(33) HOOVER R, COLE P. Temporal aspects of occupational bladder carcinogenesis. N Engl J Med 1973;288:1041–1043.

(34) COLE P, HOOVER R, FRIEDELL GH. Occupation and cancer of the lower urinary tract. Cancer 1972;29:1250–1260.

(35) SELIKOFF IJ, HAMMOND EC, SEIDMAN H. Cancer risks of insulation workers in the United States. In: Biological effects of asbestos. Lyon: IARC, 1973:209–216.

(36) BOICE JD, STONE BJ. Interaction between radiation and other breast cancer risk factors. In: International Atomic Energy Agency symposium on the late biological effects of radiation, Vienna, March 13–17, 1978. Vienna: International Atomic Energy Agency, 1978:231–247.

(37) CORREA P, CUELLLO C, DUQUE E, et al. Gastric cancer in Colombia. III. Natural history of precursor lesions. J Natl Cancer Inst 1976;57:1027–1035.

(38) JICK H, WATKINS RN, HUNTER JR, et al. Replacement estrogens and endometrial cancer. N Engl J Med 1979;300:218–222.